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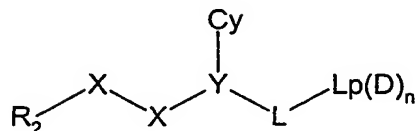
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Claims

1. A serine protease inhibitor compound of formula (I)



(I)

wherein:

R<sub>2</sub> is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, MeSO<sub>2</sub>- or R<sub>1</sub>, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R<sub>2</sub> cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR<sub>1a</sub>, C(R<sub>1a</sub>)<sub>2</sub> or NR<sub>1a</sub> group, at least one X being C, CO, CR<sub>1a</sub> or C(R<sub>1a</sub>)<sub>2</sub>;

each R<sub>1a</sub> independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R<sub>1</sub> is as defined for R<sub>1a</sub>, provided that R<sub>1</sub> is not unsubstituted aminoalkyl;

Y (the  $\alpha$ -atom) is a nitrogen atom or a CR<sub>1b</sub> group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups R<sub>3a</sub> or phenyl optionally substituted by R<sub>3a</sub> or R<sub>3i</sub>X<sub>i</sub>;

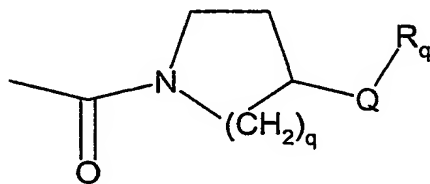
5 each R<sub>3a</sub> independently is R<sub>1c</sub>, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a  
 10 group of the formula -C(X<sup>3</sup>)N(R<sup>11</sup>)R<sup>12</sup> (wherein X<sup>3</sup> is O or S; and R<sup>11</sup> and R<sup>12</sup> are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or -OCH<sub>2</sub>O- which is bonded to two adjacent ring atoms  
 15 in Cy;

X<sub>i</sub> is a bond, O, NH or CH<sub>2</sub>;

R<sub>3i</sub> is phenyl, pyridyl or pyrimidinyl optionally substituted by R<sub>3a</sub>;

R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1j</sub> are as defined for R<sub>1a</sub>; and

20 -L-Lp(D)<sub>n</sub> is



q is 1 or 2;

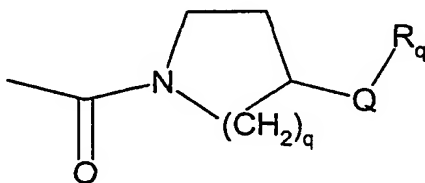
Q is methylene; and R<sub>q</sub> is NR<sub>a</sub>R<sub>b</sub> in which each of R<sub>a</sub> and R<sub>b</sub> independently is hydrogen or C<sub>1-3</sub>alkyl; or one of R<sub>a</sub> and R<sub>b</sub> is  
 25 hydrogen or methyl and the other of R<sub>a</sub> and R<sub>b</sub> is (3-6C)cycloalkyl, pyrid-4-yl, -CH<sub>2</sub>-R<sub>c</sub> or -CH<sub>2</sub>-R<sub>d</sub> in which R<sub>c</sub> is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, CONH<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or  
 30 methylsulphonyl substituent) and in which R<sub>d</sub> is isopropyl or

cyclopentyl, or  $\text{NR}_a\text{R}_b$  is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino [in which a pyrrolidino or piperidino may be a 3,4-didehydro derivative and in which a azetidino,

5 pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino may be optionally substituted on a ring carbon atom by hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl (provided that the amino, 10 hydroxy or alkoxy substituent is not on a ring carbon atom which is included in a double bond, or adjacent to a ring oxygen, sulfur or nitrogen atom) and in which the piperazino or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position];

15 or a physiologically-tolerable salt thereof.

2. A compound according to claim 1 wherein  $-\text{L-Lp(D)}_n$  is of the formula:



20 wherein:

$q$  is 1 or 2;

$Q$  is methylene; and  $\text{R}_q$  is  $\text{NR}_a\text{R}_b$  in which each of  $\text{R}_a$  and  $\text{R}_b$  independently is hydrogen or  $\text{C}_{1-3}$ alkyl; or one of  $\text{R}_a$  and  $\text{R}_b$  is hydrogen or methyl and the other of  $\text{R}_a$  and  $\text{R}_b$  is  $-\text{CH}_2-\text{R}_c$

25 or  $-\text{CH}_2-\text{R}_d$  in which  $\text{R}_c$  is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl,  $\text{CONH}_2$ ,  $\text{SO}_2\text{NH}_2$ ,

methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which  $\text{R}_d$  is isopropyl or cyclopentyl, or  $\text{NR}_a\text{R}_b$  is

30 pyrrolidino, piperidino, morpholino, piperazino, or tetrahydro-1,4-diazepino in which a pyrrolidino or piperidino

may be a 3,4-didehydro derivative and in which a pyrrolidino, piperidino, piperazino, or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position;  
or a physiologically-tolerable salt thereof.

5

3. A compound according to claim 1 or claim 2 wherein q is 2.

4. A compound according to any of claims 1 to 3 wherein

10 R<sub>q</sub> is NR<sub>a</sub>R<sub>b</sub> in which R<sub>a</sub> is hydrogen or C<sub>1-3</sub>alkyl and R<sub>b</sub> is C<sub>1-3</sub>alkyl; or R<sub>a</sub> is hydrogen and R<sub>b</sub> is (3-6C)cycloalkyl or pyrid-4-yl; or NR<sub>a</sub>R<sub>b</sub> is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino or piperazino [in which a pyrrolidino, piperidino or piperazino may be optionally  
15 substituted on a ring carbon atom by hydroxy or hydroxymethyl (provided that the hydroxy substituent is not on a ring carbon atom which is adjacent to a ring nitrogen atom) and in which the piperazino may bear a methyl group at the 4-position].

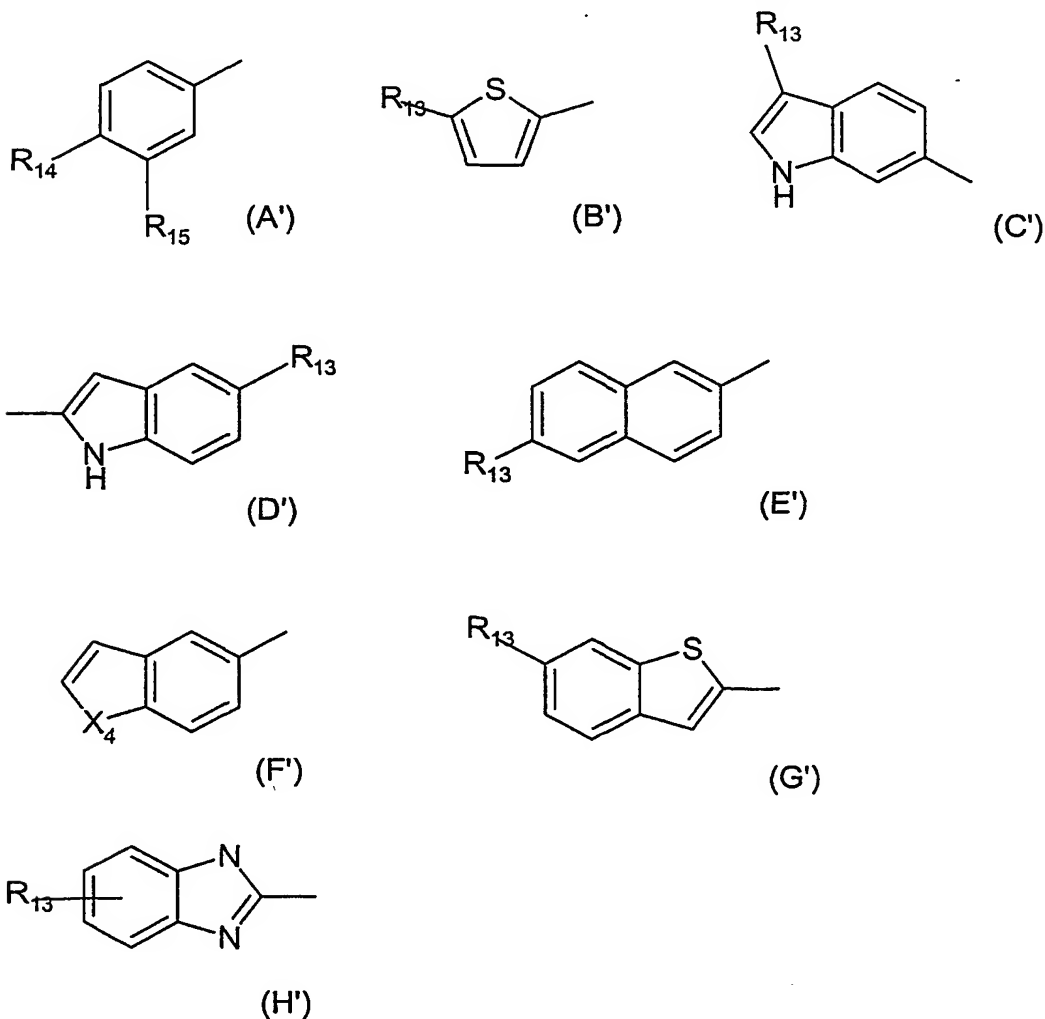
20 5. A compound according to any of claims 1 to 4 wherein R<sub>q</sub> is selected from dimethylamino, diethylamino, prop-2-ylamino, pyrrolidino, 3-pyrrolino, 3-hydroxypyrrolidino, 3-hydroxymethylpyrrolidino, piperidino, 3-hydroxypiperidino, 4-hydroxypiperidino, 4-hydroxymethylpiperidino, piperazino and  
25 4-methylpiperazino.

6. A compound according to any one of claims 1 to 5 wherein R<sub>2</sub> is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl  
30 (each of which is optionally substituted as defined in claim 1).

7. A compound according to any one of claims 1 to 6 wherein optional substituents for R<sub>2</sub> are selected from:

fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy, trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano, trifluoromethyl, methylthio, vinyl, ethynyl, acetylamino, carboxy, acetoxy, hydroxy, methyl, ethyl, amido (CONH<sub>2</sub>), 5 aminomethyl, methoxy and ethoxy.

8. A compound according to any one of claims 1 to 5 wherein R<sub>2</sub> is selected from one of the formula (A') to (H'):



wherein X<sub>4</sub> is O or S, R<sub>13</sub> is selected from hydrogen, chloro or methyl and R<sub>14</sub> is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R<sub>15</sub> is selected from hydrogen, methyl, fluoro, chloro and amino.

9. A compound according to claim 8, wherein  $R_2$  is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

10. A compound according to any one of claims 1 to 9 wherein -X-X- is -CONH-.

11. A compound according to any one of claims 1 to 10 wherein Y is CH.

12. A compound according to any one of claims 1 to 11 wherein Cy is an optionally  $R_{3a}$  substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinoloyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group substituted by  $R_{3i}X_i$  in which  $X_i$  is a bond, O, NH or  $CH_2$  and  $R_{3i}$  is phenyl optionally substituted by  $R_{3a}$ .

13. A compound according to any one of claims 1 to 12 wherein Cy is an optionally  $R_{3a}$  substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group.

14. A compound according to any one of claims 1 to 13 wherein  $R_{3a}$  is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxycarbonylamino, amino, halo, cyano, nitro, thiol,

alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula  $-C(X^3)N(R^{11})R^{12}$  (wherein  $X^3$  is O or S; and  $R^{11}$  and  $R^{12}$  are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group) and  $-OCH_2O-$  which is bonded to two adjacent ring atoms in Cy.

- 10 15. A compound according to any one of claims 1 to 13 wherein  $R_{3a}$  is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl),  
15 alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxycarbonylamino, amino, halo, cyano, nitro, thiol,  
20 alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl.

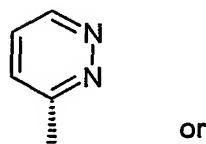
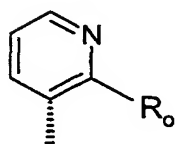
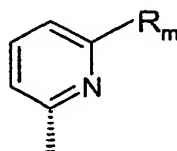
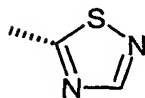
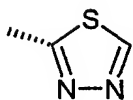
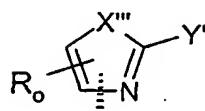
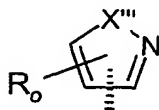
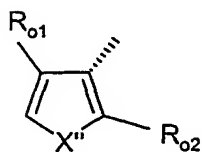
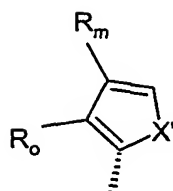
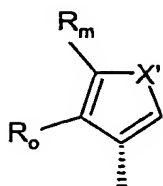
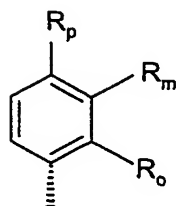
16. A compound according to any one of claims 1 to 15 wherein  $R_{3a}$  is selected from hydrogen, hydroxyl, methoxy, ethoxy,  
25 methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl,  $CONH_2$ ,  $CH_2CONH_2$ , acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro,  
30 chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, pyrrolidin-1-ylcarbonyl,



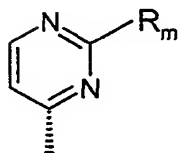
piperidin-1-ylcarbonyl or morpholin-1-ylcarbonyl and -OCH<sub>2</sub>O- (which is bonded to two adjacent ring atoms in Cy).

17. A compound according to any one of claims 1 to 16 wherein  
5 R<sub>3a</sub> is selected from hydrogen, hydroxyl, methoxy, ethoxy,  
methyl, ethyl, methylaminomethyl, dimethylaminomethyl,  
hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl,  
ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl,  
aminomethyl, CONH<sub>2</sub>, CH<sub>2</sub>CONH<sub>2</sub>, acetylamino, methoxycarbonylamino,  
10 ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro,  
chloro, cyano, nitro, thiol, methylthio, methylsulphonyl,  
ethylsulphonyl, methylsulphenyl, methylsulphonylamido,  
ethylsulphonylamido, methylaminosulphonyl,  
ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and  
15 trifluoromethyl.

18. A compound according to any one of claims 1 to 11  
wherein Cy is selected from:



or



wherein:

X' is selected from O, S and NMe;

5 X'' is selected from O and S;

X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

R\_o is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and

10 methylsulphonyl;

R\_m is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the

formula  $-C(X^3)N(R^{11})R^{12}$  (wherein  $X^3$  is O or S, and  $R^{11}$  and  $R^{12}$  are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);

5  $R_p$  is selected from hydrogen and fluoro; or

$R_o$  and  $R_m$  or  $R_m$  and  $R_p$  form an  $-OCH_2O-$  group; or

$R_o$  and  $R_m$  together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroaryl ring contains 1 or 2 heteroatoms selected from

10 nitrogen, oxygen and sulfur); and

one of  $R_{o1}$  and  $R_{o2}$  is hydrogen and the other is  $R_o$ .

19. A compound according to any one of claims 1 to 18 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 15 4-carbamoylphenyl, pyrid-2-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naphth-1-yl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl.

20. A compound as claimed in any one of Claims 1 to 19, in which the alpha atom in Y is carbon and has the conformation that would result from construction from a D- $\alpha$ -aminoacid  $NH_2-CR_{1b}(Cy)-COOH$  where the  $NH_2$  represents part of X-X.

21. A pharmaceutical composition, which comprises a compound as claimed in any one of claims 1 to 20 together with at least one pharmaceutically acceptable carrier or excipient.

22. A compound as claimed in any one of claims 1 to 20 for use in therapy.

23. Use of a compound as claimed in any one of claims 1 to 20

for the manufacture of a medicament for the treatment of a thrombotic disorder.

24. A method of treatment of a human or non-human animal body  
5 to combat a thrombotic disorder, which comprises administering  
to said body an effective amount of a compound as claimed in  
claim 1.

25. A pharmaceutical composition comprising a compound as  
10 claimed in any one of claims 1 to 20 for use to combat a  
thrombotic disorder.

26. A compound of formula I as claimed in claim 1 and named  
in any of the Examples herein, or a physiologically-tolerable  
15 salt thereof.

add  
03